REMARKS

Applicant thanks the Examiner for his assistance and insights during a telephonic interview held on November 4, 2003. During the interview, the amendments proposed herein were discussed. The Examiner requested that Applicant provide evidence of support in the Specification for the proposed amendments to Claim 1, in particular with respect to the term "proximity". Evidence of the inclusion of neurturin within the GDNF family of neurotrophins was also requested.

The requested information is supplied herein, together with supporting references for review (including a form 1449 therefor) and the inventor's Declaration under 37 CFR §1.132 (a signed copy of which will be provided). Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow, as well as those reasons set forth in the previous Amendment After Final Rejection of October 2, 2003.

A. Support for Claim Amendments: Neurotrophin Expression In, Or Within Proximity To, A Cell.

The claims have been amended to clarify that the neurotrophin-expressing vectors are administered in the invention to ensure that the neurotrophin is expressed in proximity to targeted cells. Explicit support for the "proximity" claim limitation is found in the Specification at page 2, lines 20-22.

The Examiner has questioned whether those of ordinary skill in the art will understand the meaning of the term "proximity" as it is used in the amended claims. In that respect, Applicants acknowledge that a specific definition for the word "proximity" is not provided in the Specification, beyond the disclosure of a *preferred embodiment* on page 2, lines 22-26, wherein the vectors are described as being directly introduced into the brain within 500 μm of targeted cells to intensify exposure of target cells to expressed neurotrophin.

Applicant submits, however, that those of ordinary skill in the art will recognize that the effect of expressed neurotrophin in the brain can extend to proximal cells located well outside of a 500 μm radius of the delivery site. Further, Applicant submits that those of ordinary skill in the art will understand the term "proximity," as it is used in the present claims, to refer to the phenomenon whereby neurotrophin expressed in one region of the brain influences nerve cells in proximal regions of the brain.

It is understood in the art that neurotrophin expressed in the cell body of a nerve can be transported intracellularly to distant axonal termini of the nerve, to exert biological activity in innervated regions of the brain remote from the expression site. In particular, it is now known that neurotrophins are transported within neuronal cells both in a retrograde direction (into cell nuclei) and an anterograde direction (to axonal termini). *See,* e.g., Conner, *et al., Proc. Natl. Acad. Sci. USA.*, 98: 1941–1946 (2001)(neurotrophins expressed at one site in the brain exert trophic influence over growth among neuronal populations in proximal regions of the brain); Curtis, *et al., Mol. and Cell Neurosci.*, 12:105-118 (1998) (retrograde transport of neurotrophins increases following injury to nerve cells); von Bartheld, *et al., Mol.Neurobiol.*, 24:1-28 (Humana Press, 2001) (anterograde transport of NGF and GDNF family neurotrophins and transfer thereof from axonal termini to proximal second or third order target cells); and von Bartheld, *et al., Letters to Nature*, 379:830-833 (1996)(anterograde transport and intercellular transfer of NGF family neurotrophins in the visual nervous system of chicks). Thus, a neurotrophin expressed in a cell body located at or near the delivery site for vectors utilized in the invention may exert influence over growth of axonal populations at distances well beyond the delivery site.

Further, neurotrophin transport can occur *between cells* via intercellular transport from axonal termini. *See, e.g.,* von Bartheld, *et al., Mol.Neurobiol.,* supra. As such, expression and uptake of a neurotrophin at one site in the brain can exert influence over proximal axons and neurons; i.e., those in intracellular transport and intercellular transfer communication with the

cell body in which the neurotrophin is expressed. This phenomenon is especially well demonstrated in Conner, *et al.*, supra, and in co-pending U.S. Patent Application No. 09/730,790, wherein *in vivo* delivery of a neurotrophin expressing vector into the *forebrain* influenced growth in terminal axons within the *cortex* (*see also,* data set forth in the Declaration of Dr. Mark H. Tuszynski, submitted herewith).

Clearly, therefore, a neurotrophin expressed in one site of the brain may influence proximal neuronal populations that are receptive to the neurotrophin. Such potentially receptive neuronal populations can be readily identified, given knowledge in the art of the distribution and binding characteristics of neurotrophin receptors in the brain. For example, *see,* Ebendal, *J.Neurosci.Rsch.*, 32:461-470 (1992)(review paper providing an overview of the relatively widespread distribution of trk receptors for NGF family neurotrophins throughout the brain); Sariola and Saarma, *J.Cell Sci.,* 116:3855-3862 (2003)(activity of GDNF family neurotrophin and distribution of receptors therefor in the brain). Thus, one of ordinary skill in the art will be able to identify those targeted cell populations that are receptive to a neurotrophin delivered according to the invention, and are in proximity to cells in which the neurotrophin is expressed.

It will be appreciated that this use by Applicant of "proximity" to refer to influence by expressed neurotrophins over proximal cells and cell components in the brain is consistent with the common definition of "proximity", to wit:

> The quality or state of being **next in** time, place, causation, **influence**, etc.; immediate nearness, either in place, blood or alliance.
>
> *Webster's Dictionary* (Merriam-Webster, 1998)(emphasis added).

As the Examiner is aware, absent an alternative meaning imparted by the written disclosure, terms in a patent claim are given their plain, ordinary, and accustomed meaning to one of ordinary skill in the relevant art, as of the time that the patent application was filed. *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1341, 60 USPQ2d 1851, 1854 (Fed. Cir. 2001). Such meaning may be, and often is, determined by reference to dictionary definitions, which may and often do provide claim terms with scope beyond the preferred embodiments disclosed in the specification. *Brookhill-Wilk 1, LLC. v. Intuitive Surgical, Inc.*, 334 F.3d 1294, 1298 (Fed. Cir. 2003). Therefore, the general rule is that claims of a patent are not limited to the 'preferred embodiment' disclosed in the patent specification, unless the claims are explicitly drawn to that embodiment. *Va. Panel Corp. v. Mac Panel Co.*, 133 F.3d 860, 866, 45 USPQ2d 1225, 1229 (Fed. Cir. 1997); *Comark Communications, Inc. v. Harris Corp.*, 156 F.3d 1182, 1187, 48 USPQ2d 1001, 1005 (Fed. Cir. 1998); and, *Hockerson-Halberstadt, Inc. v. Avia Group Int'l, Inc.*, 222 F.3d 951, 956, 55 USPQ2d 1487, 1491 (Fed. Cir. 2000).

Thus, consistent with its common definition, the term "proximity" as it is used in the present claims will be understood to refer **both** to cells within a 500 μm radius of the situs of neurotrophin expression (cells that, according to the preferred embodiment, can be expected to be most intensely affected by the neurotrophin), and those beyond that radius which are "influenced" by the expressed neurotrophin, via its intracellular transport and/or intercellular transfer to proximal cells and cell components.

For all of these reasons, Applicant submits that the proposed amendments to the claims to refer to the influence of neurotrophin expressed in or within proximity to a cell is both supported by the specification, and clearly understandable to those of ordinary skill in the art.

B. Support for Claim Amendments: Use of Particular Members of the GDNF Family of Neurotrophins

The Examiner has questioned whether the specification supports the newly added dependent claims (Claims 13 and 16) drawn to the use of the neurturin and persephin neurotrophins.

Support for the use of these neurotrophins in the invention is found in the Specification at page 7, line 20 through page 8, line 24, and in the Examples. In particular, the written description provides for the use of members of the GDNF family of neurotrophins. It is well-known in the art that the GDNF family of neurotrophins is comprised of GDNF, neurturin, persephin and artemin. *See, e.g.,* Sariola and Saarma, *J.Cell Sci.,* 116:3855-3862 (2003)(review paper providing an overview of the nature and activity of members of the GDNF family of neurotrophins).

Applicant therefore respectfully submits that the specification provides clear, unambiguous support for claims drawn to the use of members of the GDNF family of neurotrophins, including neurturin and persephin.

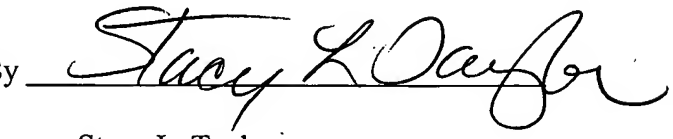
CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner has graciously agreed to a further telephonic interview with respect to this application, now scheduled for January 6, 2003 at 2:00 p.m., Eastern Standard Time. However, the Examiner is invited to contact the undersigned by telephone in the interim if it is felt that an earlier discussion would advance the prosecution of the present claims.

Date: December 30, 2003

Respectfully submitted,

By 

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